UCI Office of Research	**Institutional Review Board** **Human Research Protections** **Protocol Narrative – Expedited/Full Committee Biomedical/Clinical Research** *Version April 2021*
Upload this completed narrative and any supplemental documentation to the IRB Application.	**IRB USE ONLY –** **HS#: 2021-6732**
Lead Researcher Name: Alexandre Chan, PharmD, MPH	
Study Title: Electroacupuncture for the management of symptom clusters in cancer patients and survivors (EAST): A feasibility study	

CLINICAL TRIAL MASTER PROTOCOL AND INVESTIGATIONAL BROCHURE INFORMATION *

	Master Protocol	Investigator Brochure:	Investigator Brochure:	Sponsor Consent Form Template(s)
Version #:	N/A	N/A	N/A	N/A
Version Date:	N/A	N/A	N/A	N/A

[X] This study is investigator-authored (investigator developed the study and is conducting the study at UCI and/or with other non-UCI sites).

NON-TECHNICAL SUMMARY

Provide a brief non-technical summary or synopsis of the study that can be understood by IRB members with varied research backgrounds, including non-scientists and non-affiliated members.

This is a sham-controlled, patient and assessor-blinded pilot trial to evaluate the feasibility of administering EA as an intervention for symptom clusters in cancer patients and survivors, and to evaluate the degree that EA could reduce symptom clusters and the possible underlying mechanisms through examining its influence on biomarkers that are linked with the symptoms.

Participants will be randomized to either the treatment arm (those who will receive EA) or the control arm (those who will receive sham-EA). The treatment period for both groups will be 10 weeks. There will be one study visit a week over the course of the 10-week treatment period, for a total of 10 study treatment visits. Participants in the treatment arm will receive EA at 13 standardized acu-points that have been chosen for their therapeutic effects. Participants in the control arm will receive electrical stimulation at non-disease acu-points. There will be four data collection time points for each participant: (1) baseline, (2) mid-treatment (5 weeks from baseline), (3) end of treatment (10 weeks from baseline), and (4) 4 weeks after end of treatment (14 weeks from baseline). At each of these timepoints, 10mL of peripheral blood will be collected for a biomarker analysis and participants will be

asked to complete 4 questionnaires and a computerized cognitive test to evaluate their cognitive function, fatigue level, insomnia, psychological distress, and quality of life. In total, study participation will last for 14 weeks.

SECTION 1: PURPOSE AND BACKGROUND OF THE RESEARCH

1. Provide the scientific or scholarly rationale for the research. Describe the relevant background information and the specific gaps in current knowledge that this study intends to address.

In 2019, it was estimated that approximately 16.9 million US individuals with a history of cancer are alive and cured of cancer. With the advent of therapeutics in cancer and improved early detection of first malignancies, the number of cancer survivors is predicted to increase drastically over the next decade. Unfortunately, many survivors of cancer often experience a range of physical symptoms and psychosocial burden throughout and after chemotherapy treatment, of which fatigue, cognitive impairment, insomnia, and psychological distress are often the most prevalent. For example, **up to 49% of all breast cancer patients experience co-occurring symptoms, a phenomenon known as 'symptom clustering', implying the great overlaps of cognitive, affective, and somatic symptoms.** There is a large amount of evidence in the literature describing how these symptoms co-occur in cancer survivors. For example, there is strong evidence to support determinants of psychological distress (anxiety and depression) and cancer-related fatigue as predictors for perceived cognitive functioning. Similarly, somatic symptoms of fatigue and sleep disturbance can lead to mood disturbance, which may also contribute to cognitive disturbances.

The novel insights into the immune-oncological mechanisms underlying symptom clusters allow us to understand why these symptoms often co-occur in cancer patients. Biologically, stress, mood changes, fatigue and cognitive changes are part of the "cytokine-induced sickness behavior" observed in cancer patients. **Pro-inflammatory cytokine irregularities and mitochondria dysfunction are associated with cognitive complaints, depression, anxiety, and fatigue.** Particularly, high IL-6 is associated with poor executive function, whereas IL-6, IL-1RA, and TNF-α levels relate to fatigue ratings. Recent work has also suggested that chemotherapy leads to dysregulation of cytokines, which may provoke a neuroimmunoendocrine response that affects patients' mood and cognitive performance.

Management of symptom clusters remains a significant challenge within the cancer care community. Firstly, none of the current pharmacological therapies are capable to tackle multiple symptoms that patients are experiencing concurrently. For example, current pharmacological therapies to treat anxiety (such as benzodiazepines) are very specific to target a symptom and are unlikely to provide benefits for co-occurring symptoms such as fatigue and cognitive impairment. Likewise, although hypnotics (such as diphenhydramine or melatonin) are frequently prescribed to cancer patients and provide rapid relief to insomnia, however, they can also lead to other symptoms such as fatigue and cognitive impairment. Non-pharmacological modalities, such as exercise, have been routinely recommended by guidelines to manage symptoms such as cancer-related fatigue in cancer patients. However, the most ideal exercise regimen to recommend is currently unknown, and the needed potency in order to provide adequate symptomatic relief is unclear at this time.

Over the past few years, there is a significant growth of integrative oncology within cancer care. Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, including acupuncture, alongside conventional cancer treatments. **To address the current gaps in managing symptom clusters within cancer patients, integrative health practices such as acupuncture hold great potential.** Currently, guidelines are recommending the use of acupuncture to manage individual symptoms such as mood disturbances, fatigue, and pain. An improved variation of acupuncture, namely electroacupuncture (EA), is gaining traction within integrative health practices.

Current literature suggests that EA is more beneficial than traditional acupuncture to provide symptom relief. The clinical benefits associated with EA are likely to span across multiple symptom domains with synergistic effect. **However, there is a lack of clinical studies to evaluate whether EA is beneficial for managing multiple co-occurring symptoms in cancer patients.** Hence, we designed this pilot trial to study whether it is feasible to administer EA as an intervention for symptom clusters in our cancer population, and to evaluate the degree that EA could reduce symptom clusters and the possible underlying mechanisms through examining its influence on biomarkers that are linked with the symptoms.

2. Provide relevant preliminary data (animal and/or human).

1. **Using patient-reported outcome tools to assess symptom clusters in cancer patients**: We have optimized the numerous tools that will be used in our proposed study to describe the various cancer-related symptoms. Moving forward, these robust tools will be incorporated into the proposed study to ensure that we are accurately capturing the symptoms. This includes the Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog) v.3.0, Multidimensional *Fatigue* Syndrome Inventory-Short Form (*MFSI*-SF)[4] and Rotterdam Symptom Checklist (RSCL). Psychometrics and minimally clinical differences were established for all the tools.

2. **Symptom clustering and employment interference in breast cancer patients and survivors:** To study how cancer-related symptoms co-occur in patients, we have conducted 2 studies. In a longitudinal cohort study of 131 breast cancer patients receiving chemotherapy, self-reported cognitive impairment was strongly associated with anxiety, fatigue, and biomarkers. More importantly, when we trended the trajectory of the four symptoms (cognition, fatigue, anxiety, and insomnia) over 15 months, we reported that the symptom profiles were very similar, suggesting that these symptoms are likely to co-occur, confirming the characteristics of symptom clustering. In another study, higher sleep disturbance scores were associated with both initial and ongoing employment interference in breast cancer patients. Survivors of breast cancer experience difficulty returning to normalcy as they are affected by poorly managed symptoms.

3. **Evaluating symptom-related biomarkers:** We have conducted numerous translational studies to evaluate the associations between various biomarkers and cancer-related symptoms in patients, providing us potential targets for our EA intervention.

Biomarker	Findings
Proinflammatory Cytokines	Elevation of TNF-α is associated with cognitive impairment and cancer-related fatigue during chemotherapy[4], while elevation of IL-6 and IL-8 was associated with persistent cognitive impairment post-chemotherapy in survivors.
Brain-derived neurotropic factor (BDNF)	Patients with higher plasma BDNF levels at the end of chemotherapy had lower odds of developing persistent overall subjective CRCI (OR = 0.74; 95% CI = 0.57–0.97) and persistent CRCI in the functional interference domain (OR = 0.62; 95% CI = 0.39–0.98).
Mitochondria DNA	Reduction of mtDNA level was associated with 4% increased risk for worsening of CRF.

Based on our previous prospective cohort study (Ng et al. 2017) which characterized the long-term trajectory of self-perceived cognitive impairment among early-stage breast cancer patients, we observed that approximately half of the breast cancer patients reported cognitive impairments during and post-chemotherapy, and up to one-third experienced deficits at 15 months post-treatment. In another study that interviewed breast cancer patients via focus group discussions (Cheung et al. 2012), many of them

experienced memory loss, difficulty in decision making and speech problems after chemotherapy which had affected their quality of life. In another cohort study, we have observed that 1 out of 4 (23.8%) of the cancer patients experienced clinically significant fatigue after chemotherapy. (Toh et al., 2019) CRCI, CRF and insomnia are real but insidious complications of cancer and chemotherapy that need to be managed during cancer treatment and survivorship care.

3. Describe the purpose, specific aims or objectives. Specify the hypotheses or research questions to be studied.

The purpose of this study is to investigate the efficacy, safety, and feasibility of offering EA as an intervention to improve cancer-related symptoms (cognitive impairment, fatigue, psychological distress and insomnia) and quality of life among cancer patients and survivors receiving care at UCI Health. In addition, changes in biomarkers (plasma BDNF, pro-inflammatory cytokines and mitochondrial DNA) known to be associated with cancer-related symptoms. We hypothesize that EA is an effective, safe, and feasible intervention for cancer patients and survivors.

Our specific aims are as follows:

1. To compare the efficacy of EA versus sham-EA control in reducing cognitive toxicity, fatigue, psychological distress, insomnia and quality of life.
2. To evaluate the impact of EA versus sham-EA control on biomarkers, including circulating BDNF, pro-inflammatory cytokines (IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-alpha), mitochondrial DNA (oxidative stress indicator), and safety.

To assess the feasibility of administering EA to manage symptom clusters in cancer patients.

4. Describe the primary outcome variable(s), secondary outcome variables, and predictors and/or comparison groups as appropriate for the stated study objectives/specific aims.

Primary outcome variable:

- **Subjective cognitive function –** All subjects will complete the FACT-Cog version 3 questionnaire to assess self-perceived subjective cognitive function.

Secondary outcome variables

- **Objective cognitive function –** All subjects will complete CANTAB®, to assess objective cognitive functions. CANTAB® is a computerized cognitive testing software to assess various cognitive domains. Both subjective and objective assessments are recommended by the International Cognition and Cancer Task Force (ICCTF).
- **Fatigue –** MFSI-SF is a validated questionnaire that comprises of 30 items and contains 5 subscales, each with 6 items: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor.
- **Psychological distress and insomnia** – The Rotterdam Symptom Checklist (RSCL) will be used to measure the psychological symptoms (anxiety and depression) and insomnia. Psychological distress is indicated by a score of >16 in the psychological domain. Insomnia is measured by a single item in the checklist.
- **Quality of life –** EORTC QLQ-30 is a validated questionnaire developed to assess cancer patients' health-related quality of life. It incorporates 5 functional scales (cognitive, emotional, physical, role, and social), symptom scales (e.g. pain, fatigue, insomnia), and a global health scale.
- **Safety monitoring** – Participants will be monitored for adverse events such as bruising, pain or discomfort, bleeding and possible infections. Severity are graded according to the Common Terminology Criteria for Adverse Events V5.
- **Biomarkers – <u>Plasma BDNF and cytokines</u>** (IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-alpha) levels will be quantified using commercially available ELISA kits. **<u>Mitochondrial DNA</u>** will be quantified using the quantitative PCR method.

- **Feasibility of EA (recruitment, compliance, blinding and patient acceptance)**
    - ***Recruitment:*** Recruitment will be evaluated as the number of participants recruited (% of target recruitment) and rate of recruitment a month. Reasons for declining the participation will also be documented. Additionally, time spent on recruitment will be examined to assess recruitment productivity.
    - ***Compliance:*** Compliance is measured as the number of acupuncture sessions successfully completed, and the proportion of participants completing the scheduled acupuncture sessions.

Blinding and patient acceptance: all study participants will complete a questionnaire evaluating their perceptions towards the EA treatment at the end of study period. Participants will be asked whether they believe that they have received EA or sham-EA, if they are satisfied and benefited from the treatment, and whether they would consider undergoing treatment again outside of a trial setting.

5. List up to ten relevant references/articles to support the rationale for the research. Do not append an extensive NIH-grant-style bibliography.

1. Janelsins, M.C., et al., Cognitive Complaints in Survivors of Breast Cancer After Chemotherapy Compared With Age-Matched Controls: An Analysis From a Nationwide, Multicenter, Prospective Longitudinal Study. J Clin Oncol, 2017. 35(5): p. 506-514.
2. Ng, T., et al., Distinct and heterogeneous trajectories of self-perceived cognitive impairment among Asian breast cancer survivors. Psychooncology, 2018. 27(4): p. 1185-1192.
3. Cheung, Y.T., et al., Association of proinflammatory cytokines and chemotherapy-associated cognitive impairment in breast cancer patients: a multi-centered, prospective, cohort study†. Annals of Oncology, 2015. 26(7): p. 1446-1451
4. Toh YL, et al. Association of plasma leptin, pro-inflammatory adipokines and cancer-related fatigue in early-stage breast cancer patients: A prospective cohort study. J Cell Mol Med. 2019;23:4281–4289.
5. Cheung, Y.T., et al., Effects of chemotherapy and psychosocial distress on perceived cognitive disturbances in Asian breast cancer patients. Ann Pharmacother 2012. 46(12): p. 1645-55.
6. Liou, K.T., et al., Effects of acupuncture versus cognitive behavioral therapy on cognitive function in cancer survivors with insomnia: A secondary analysis of a randomized clinical trial. Cancer, 2020. 126(13): p. 3042-3052.
7. Zhang, Z.J., et al., Electroacupuncture trigeminal nerve stimulation plus body acupuncture for chemotherapy-induced cognitive impairment in breast cancer patients: An assessor-participant blinded, randomized controlled trial. Brain Behav Immun, 2020. 88: p. 88-96.
8. Tong, T., et al., Efficacy of Acupuncture Therapy for Chemotherapy-Related Cognitive Impairment in Breast Cancer Patients. Med Sci Monit, 2018. 24: p. 2919-2927.
9. Zeng, Y., et al., Effects of Acupuncture on Cancer-Related Cognitive Impairment in Chinese Gynecological Cancer Patients: A Pilot Cohort Study. Integr Cancer Ther, 2018. 17(3): p. 737-746.
10. Cheung Y.T., et al. Cognitive changes in multiethnic Asian breast cancer patients: a focus group study. Ann Oncol, 2012. 23(10): p. 2547-2552.

SECTION 2: ROLES AND EXPERTISE OF THE STUDY TEAM

1. **List the Lead Researcher and Co-Researchers who will engage in human subject research.** *Co-Researchers are faculty, staff, students and other academic appointees who the Lead Researcher (LR) considers to be key personnel for conducting the research study. These individuals work closely with the LR to design, conduct, and/or report on the research.*
2. ***UPDATED!*** **List Research Personnel as required per the Research Personnel Heat Map.**
3. **In lieu of listing Research Personnel (as required per the Research Personnel Heat Map), the LR must maintain the Study Team Tracking Log (or something similar) listing all Research Personnel who are engaged in the research.**
4. For each research team member, indicate all applicable research activities the individual will perform. *Finalizing informed consent is reviewing, answering/asking questions, confirming competency, as necessary, and signing/confirming the informed consent.*
5. If applicable, list the Faculty Sponsor as a Co-Researcher who will have research oversight responsibilities.

Lead Researcher:

Name and Degree: Alexandre Chan, PharmD

Position/Title and Department: Professor and Founding Chair, Clinical Pharmacy Practice

Team Member will: **[X]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Dr. Chan will have oversight over the study. He will participate in the screening and recruitment of patients who are deemed eligible at Chao Family Comprehensive Cancer Center. He will be responsible for the finalization of consent. He will also oversee the collection of data, the blood draws, and will participate in data analysis and data reporting.

Dr. Chan is a Founding Chair and Professor in Clinical Pharmacy at School of Pharmacy & Pharmaceutical Sciences. He has over 15 years of experience in studying cancer supportive care and survivorship issues, specifically in the areas of cancer-related cognitive impairment and cancer-related fatigue. Dr. Chan is also experienced with the design of clinical research studies in Integrative Oncology. Currently he is serving as a Principal Investigator (PI) for a clinical trial that utilizes an herbal admixture for management of cancer-related fatigue (Clinicaltrials.gov: NCT04104113). He has also conducted studies evaluating complementary alternative medicines use in patients diagnosed with cancer. He has published >200 peer review manuscripts in his academic career, with >40 peer reviewed papers in the areas of cancer supportive care and survivorship (such as cancer-related cognitive impairment [CRCI] and cancer-related fatigue), with a focus on the prevalence, biomarkers and management of CRCI. Currently, Dr. Chan is a co-Chair for the CRCI study group under the Multinational Association Supportive Care in Care.

Co-Researcher:

Name and Degree: Shiasta Malik MD

Position/Title and Department: Professor, School of Medicine

Team Member will: **[ ]** serve as Faculty Sponsor with research oversight responsibilities

[X] Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities **[ ]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Dr. Malik is the Associate Vice Chancellor in Integrative Health as well as the Executive Director at the Susan and Henry Samueli College of Health Sciences. Dr. Malik has managed two previous acupuncture R01s as co-PI (R01AT009247 and R01HL072125) and has clinical trial experience from other NIH-funded as well as foundation-funded studies on the use of acupuncture.

Dr. Malik will participate in patient recruitment. She is instrumental in the design of the protocol and will function as a blinded data accessor. She will not have access to the subject identifiable data but will review data and assist with manuscript preparation.

Co-Researcher:

Name and Degree: Lifang Xie PhD

Position/Title and Department: Acupuncturist, Susan Samueli Integrative Health Institute

Team Member will: **[ ]** Screen/Recruit **[X]** Finalize Informed Consent

[X] Perform Research Activities **[ ]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Dr. Xie is a Clinical Assistant Professor and licensed acupuncturist who leads the research acupuncturist team at UCI Cardiovascular Acupuncture Research Program (CARP). She practices at the Susan Samueli Integrative Health Institute. Dr. Xie will provide acupuncture treatment to the subjects as described in the protocol.

Co-Researcher:

Name and Degree: Ritesh Parajuli, MD

Position/Title and Department: Assistant Clinical Professor at Division of Hematology Oncology, Chao Family Comprehensive Cancer Center

Team Member will: **[X]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities **[ ]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Dr. Parajuli is an Assistant Clinical Professor at Division of Hematology Oncology, Chao Family Comprehensive Cancer Center. He serves as the medical director of the Infusion Center at the NCI

Designated Chao Family Comprehensive Cancer Center, as well as the Co-Chair of the Breast Disease Oriented Team at the Cancer Center.

Dr. Parajuli will participate in patient recruitment and will assist with study design. He will not have access to the subject identifiable information but will review data and assist with manuscript preparation.

Research Personnel:

Name and Degree: Paul H. Coluzzi, MD, MPH

Position/Title and Department: Clinical Professor of Medicine at Division of Hematology Oncology, Chao Family Comprehensive Cancer Center

Team Member will: **[X]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities **[ ]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Dr. Coluzzi has a strong interest in supportive and survivorship care, and he sees patients at the Chao Family Comprehensive Cancer Center in Orange, at UCI Health Pacific Breast Care Center in Costa Mesa and at UCI Health — Yorba Linda. Dr. Coluzzi is involved in the design of the study as well as identifying appropriate subjects for recruitment and will assist with the analysis of final data and manuscript preparation.

Research Personnel:

Name and Degree: Argyrios Ziogas, PhD

Position/Title and Department: Associate Professor of Epidemiology/Biostatistics

Team Member will: **[ ]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities **[ ]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Dr. Ziogas is an Associate Professor of Epidemiology/Biostatistics. Dr. Ziogas will provide biostatistics support for the planned study, as well as providing guidance with the sample size calculation. He is involved with the design of the study and the analysis of final data.

Research Personnel:

Name and Degree: Ding Quan (Quinton) Ng BSc (Pharm) (Hons)

Position/Title and Department: Graduate Student Researcher, Clinical Pharmacy Practice

Team Member will: **[X]** Screen/Recruit **[ ]** Finalize Informed Consent

[X] Perform Research Activities **[X]** Access subject identifiable data

List the research activities/procedures to be performed and the individual's relevant qualifications (training, experience):

Ding Quan is a graduate research assistant who is a part of Dr. Chan's research team. He will assist with patient screening, scheduling, and communication. Additionally, he will assist with the collection of data during study visits (administration of study questionnaires), disbursement of compensation for

participation, collection, and analysis of biospecimens. Finally, he will assist with the analysis and reporting of the data as well as manuscript preparation.

SECTION 3: SUBJECT POPULATION(S) (INDIVIDUALS/RECORDS/BIOSPECIMENS)

A. Subjects To Be Enrolled on this UCI protocol (Persons/Records/Biospecimens)

1. Complete the table of subject enrollments below. *Include additional rows for subject category/group, as needed.*
2. If the study involves the use of existing records or biospecimens, specify the maximum number to be reviewed/collected, and the number needed to address the research question.

Category/Group (e.g., adults, controls, parents, children)	**Age Range** (e.g., 7-12, 13–17, adults)	**Maximum Number to be Consented or Reviewed/Collected** (include withdrawals and screen failures)	**Number Expected to Complete the Study *or Needed to Address the Research Question***
Adult cancer patients	≥ 18	64	58
		Total: 64	

B. Overall Study Sample Size

If this is a multi-site study, provide the total number of subjects to be enrolled from all sites.

[X] Not applicable: This study will only take place at UCI, and does not involve other sites.

Total number of subjects across all sites: N/A

C. Eligibility Criteria

1. Identify the criteria for inclusion and exclusion.

Patients

Inclusion criteria

- Patients diagnosed with cancer that have received anti-cancer treatment within the past one year
- ≥ 18 years of age
- Life expectancy ≥ 6 months
- Complaints of two or more of the following symptoms (fulfilling the definition of a symptom cluster): memory impairment/attention deficit, fatigue, insomnia, depression, or anxiety over the past 7 days
- Able to provide informed consent to participate in the study.

Exclusion criteria

- Presence of metastasis
- Severe needle phobia
- Psychiatric or medical disorders which would affect cognitive assessments, such as, dementia, Alzheimer's disease, a history of any neurological condition, traumatic brain injury, stroke, and the use of psychotropic medication
- Known bleeding disorder (e.g. hemophilia, Von Willebrand's disease, thrombocytopenia)
- Has pacemaker or other electronic metal implants
- Epilepsy
- Already receiving acupuncture therapy or received acupuncture treatment in the past 3 months.
- Breastfeeding, pregnant or are planning get pregnant during the study period

2. If eligibility is based on age, gender, pregnancy/childbearing potential, social/ethnic group, or language spoken (e.g., English Speakers only), provide a scientific rationale.

[ ] Not applicable: Subject eligibility is not based on these factors.

The risk of EA or sham-EA on a newborn or an unborn child is unknown. As such, we will exclude patient who are breastfeeding, pregnant or are planning to get pregnant during the study period. This study is restricted to patients who are 18 years or older, as only adult patients are seen by Dr. Xie at the Susan Samueli Integrative Health Institute.

3. If American Indian or Alaska Native Tribes will be included in the research:
   a. Specify the name of the Tribe and
   b. Specify whether there is Tribal Law that may be applicable to this research and that provides additional protections for subjects (i.e., additional information to be disclosed in the consent process).

[X] Not applicable: American Indian or Alaska Native Tribes are not included in the research.

D. PRE-SCREENING AND DETERMINING ELIGIBILITY WITHOUT INFORMED CONSENT

1. **IMPORTANT NOTES:**
   a. This section is **Not applicable** to research that is funded/supported by the Department of Justice (**DOJ**)
   b. This section addresses pre-screening activities that are performed **without the written informed consent of the prospective subject or legally authorized representative (LAR).** This may be allowed without requesting a waiver of informed consent **IF the following guidelines are utilized**:

[ ] Not applicable: Information and/or biospecimens will not be obtained for the purpose of screening, recruiting, or determining eligibility of prospective subjects. *Skip to Section 4.*

[ ] Study team will obtain information through **oral or written communication** with the prospective subject or LAR (i.e. self-report of medical information; medical records will not be screened).

*Submit recruitment script/s for IRB approval. Be sure to address minimum recruitment requirements and address **the following guidelines**:*

i. Privacy: The script must address the case where someone other than the potential subject receives the communication. Please be mindful of privacy considerations (i.e., do not

disclose any private information – such as a patient diagnosis). Limit phone contact / messages to no more than 5 attempts.

ii. *Expertise: Study team member/s contacting potential subject must be knowledgeable and able to answer questions related to the screening and the main study.*

iii. *Specific Information: Include a description of the information and/or biospecimens that will be obtained for the purpose of screening, recruiting, or determining eligibility and the reasons for performing the screening tests.*

iv. *Confidentiality: Include a statement that informs the potential subject that if they are not eligible to participate in the study that the identifiable information and / or biospecimens will not be used for research purposes and will be destroyed at the earliest opportunity consistent with conduct of the research.*

[X] Study team will **screen medical records** to determine subject eligibility.

Complete Appendix T to request a partial waiver of HIPAA Authorization.

[ ] Study team will **screen medical records** to determine subject eligibility **under IRB approved screening protocol.** Specify HS#: <Type here>

[ ] Study team will **screen non-medical records** (i.e., student records) to which they have access to determine subject eligibility. Specify: <Type here>

[ ] For research accessing student records, check here to confirm that evidence of FERPA[1] compliance has been / will be obtained (and on file) from the local school/district site or the UCI Registrar prior to the initiation of research.

[ ] Study team will **access stored identifiable biospecimens**.

2. For studies that will **screen medical records**, explain how the study team will access the clinical data. *Access to UCI Medical Center medical records for research purposes outside the capacity of the Honest Broker Services, such as access to physician notes, must be obtained from the Health Information Management Services.*

[1] *34 CRF 99: Family Educational Rights and Privacy Act (FERPA) applies to this research.*

[ ] Not applicable: This study does not involve the screening of medical records.

How Obtained: Indicate <u>all</u> that apply:
[X] The study team will request specific patient information/data from UCIMC Health Information Management Services.

[X] The study team will review their UCI patients' records and abstract data directly from those records.

[ ] The study team will request specific patient information/data from UCI Health Honest Broker Services. Describe the following:

Cohort selection criteria (e.g., use the available Clinical Terms from the Cohort Discovery Tool such as Demographics: Gender, Diagnoses: Asthma, Procedures: Operations on digestive system): <Type here>

Expected cohort size/patient count: <Type here>

Cohort attributes or data elements (e.g., lab test values, medication, etc.): <Type here>

[ ] The study team will review non-UCI Health records and abstract data directly from those records. Describe the following:

Specify the non-UCI Health records that will be screened: <Type here>

Explain how the study team has access to this clinical data: <Type here>

[ ] Other; explain: <Type here>

3. For studies that will **screen existing biospecimens**:
    a. Indicate the source of the biospecimens and explain how the existing biospecimens will be obtained.
    b. Indicate whether the biospecimens were originally collected for research purposes.

[X] Not applicable: This study does not screen existing biospecimens.

How Obtained: Indicate all that apply:
[ ] UCI Health Pathology Biorepository

[ ] Other UCI-Health Entity; specify: <Type here>

[ ] Non-UCI Entity; specify: <Type here>

[ ] Other; explain: <Type here>

Originally collected for research purposes:
[ ] NO – Please explain: <Type here>

[ ] YES – UCI IRB approval granted under IRB protocol number (i.e. HS#): <Type here>

[ ] YES – Non-UCI IRB approval granted. Confirm **one** of the following:

[ ] A copy of the IRB Approval Notice and Consent Form for the original research collection will be submitted with the IRB application (APP). The IRB Approved Consent Form does not preclude the proposed activity.

[ ] A copy of the commercial Vendor Policy or a Letter from the Vendor attesting that the information was collected and will be shared in an appropriate and ethical manner will be submitted with the APP. The vendor's policy does not preclude the proposed activity.

SECTION 4: RECRUITMENT METHODS

Check any of the following methods that will be used to recruit subjects for this study:
[ ] Not applicable: This study involves no direct contact with subjects (i.e., use of existing records, charts, biospecimens). Specify database or IRB-approved protocol number (HS#), if applicable: <Type here>
[ ] Advertisements, flyers, brochures, email, Facebook, and/or other media. Specify where recruitment materials will be posted: <Type here> If subjects will be recruited by mail, e-mail, or phone, specify how their contact information will be obtained: <Type here>    *Submit recruitment materials for IRB approval.*
[X] The study will be listed on Clinicaltrials.gov. *All Applicable Clinical Trials must be registered.*
[X] The study will be listed on the Center for Clinical Research (CCR) Find a Trial web page. *This webpage is for UCI School of Medicine departments as well as the clinical research conducted at the Chao Family Comprehensive Cancer Center and the Alpha Stem Cell Center.*

[X] The study will be listed on the UC Irvine Health Clinical Trials web page.

Submit the UCIMC Standard Research Recruitment Advertisement for IRB approval.

[ ] The UCI Social Sciences Human Subjects Lab/Sona Systems will be used.

Ensure that all applicable consent documents include reference to use SONA.

[X] Referral from colleagues

- Study team will provide colleagues with UCI IRB-approved recruitment materials for distribution to potential subjects (e.g., recruitment flyer, introductory letter);
- An IRB-approved recruitment letter will be sent by the treating physician. The letter will be signed by the treating physician and sent to his/her patients to inform them about how to contact study team members; and/or
- Colleagues obtain permission from interested patient to release contact information to researchers.
- Study team does not have access to patient names and addresses for mailing.
- If colleagues will screen their patients' medical records to determine subject eligibility and approach patients directly about study participation: *Complete Appendix T to request a partial waiver of HIPAA Authorization.*

Submit recruitment materials for IRB approval.

[ ] Study team will contact potential subjects who *have given prior permission to be contacted* for research studies.

Specify when and how these individuals granted permission for future contact: <Type here>

Specify database or IRB-approved protocol number (HS#): <Type here>

[ ] Study team members will approach their own patients, students, employees for participation in the study.

[ ] Other Recruitment Methods: <Indicate the recruitment method(s) here>

SECTION 5: INFORMED CONSENT PROCESS

A. Methods of Informed Consent

1. Indicate all applicable informed consent methods for this study. *Submit the consent/assent document(s) with your e-IRB Application (e.g., Study Information Sheet, Recruitment script, Consent Form, etc.). Only IRB approved consent forms (containing the IRB approval footer) may be used to consent human subjects at UCI.*

[X] Signed informed consent will be obtained from subjects. Signed informed consent and/or parental permission will be obtained from subjects, as applicable.

[ ] Requesting a waiver of signed informed consent. Signed consent will not be obtained; consent will be **obtained verbally or via the web**. Informed consent, parental permission and/or child assent will be obtained from subjects, as applicable.

Complete Appendix P.

[ ] Requesting to seek surrogate consent from the subjects' LAR. Surrogate consent may be considered only in research studies relating to the cognitive impairment, lack of capacity or serious or life-threatening disease and conditions of the research subjects.

Complete Appendix E.

[ ] Requesting a waiver of the consent process. Consent will not be obtained. *Skip to Section 5.B.*

Complete Appendix O.

2. Indicate where the consent process will take place.

[X] In a private room
[ ] In a waiting room
[ ] In an open unit
[ ] In a group setting
[ ] The internet
[ ] In public setting
[ ] Over the phone
[ ] Other (specify): <Type here>

3. Specify how the research team will assure that subjects or their LAR have sufficient time to consider whether to participate in the research.

[X] Subjects or their LAR will be allowed to take home the unsigned consent form for review prior to signing it.

[ ] Subjects or their LAR will be allowed <Type here> hours to consider whether to consent.

[ ] Other (specify): <Type here>

4. If children are enrolled in this study, describe the parental permission process and the child assent process.

[X] Not applicable: Children are not enrolled in this study.

5. Some subjects may be vulnerable to coercion or undue influence, such as those who are economically or educationally disadvantaged, have impaired decision-making capacity, or students (undergraduate, graduate, and medical students) and employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.), describe the procedures to ensure the voluntary participation of these individuals.

[X] Not applicable: Subjects are not vulnerable to coercion or undue influence.

[ ] Other (specify): <Type here>

B. Health Insurance Portability and Accountability Act (HIPAA) Authorization

Indicate all applicable HIPAA authorization methods for this study.

[ ] Not applicable: Study does not involve the creation, use, or disclosure of Protected or Personal Health Information (PHI).

[ ] Requesting a Total waiver of HIPAA Authorization. HIPAA authorization will not be obtained at all for the study.

Complete Appendix T.

[X] Requesting a Partial waiver of HIPAA Authorization. HIPAA authorization will not be obtained for screening/recruitment purposes. However, written (signed) HIPAA research authorization is obtained for further access to personal health information.

Complete Appendix T.

[ ] Written (signed) HIPAA Research Authorization will be obtained from subjects. Signed authorization, parental authorization, and/or child assent will be obtained from subjects or their LAR, as applicable.

Complete the HIPAA Research Authorization form.

C. Methods of Informed Consent for non-English Speakers

1. Indicate the applicable informed consent method for non-English speakers.

[ ] Not applicable: Only individuals who can read and speak English are eligible for this study. *Scientific justification must be provided in Section 3.C.2.*

[X] The English version of the consent form will be translated into appropriate languages for non-English speaking subjects or their LAR once IRB approval is granted. *The translated consent form must be submitted to the IRB for review prior to use with human subjects. Only IRB approved consent forms (containing the IRB approval stamp) may be used to consent human subjects at UCI.*

[ ] Requesting a short form consent process.

Complete Appendix Q.

The short form process will be used for the following occasional and unexpected languages:

[ ] All non-English languages
[ ] All non-English languages except Spanish
[ ] Other languages (specify): <Type here>

2. Explain how non-English speaking subjects or their LAR will be consented in their language and who will be responsible for interpreting and facilitating the informed consent discussion for the non-English speaking subjects.

[ ] At least one member of the study team is fluent in the language that will be used for communication, and that study team member(s) will be available during emergencies.

For all members of the study team responsible for obtaining informed consent from non-English speaking subjects, provide their qualifications to serve in this capacity (i.e. language fluency) in Section 2.

[X] The study team has 24-hour access to a translation service with sufficient medical expertise to discuss the research in this study.

[ ] Other (explain): <Type here>

SECTION 6: RESEARCH METHODOLOGY/STUDY PROCEDURES

A. Study Location

Specify where the research procedures will take place (e.g. UCI Douglas Hospital – Cardiac Care Unit, UCI Main Campus Hewitt Hall, UCI Health – Pavilion II, UCI Family Health Center, Anaheim, Irvine High School).

If research activities will also be conducted at non-UCI locations (e.g., educational institutions, businesses, organizations, etc.), Complete Appendix A. Letters of Permission or other documentation may be required (e.g. Off-site Research Agreements or IRB Authorization Agreements).

Subjects will be recruited from the UCI Chao Family Comprehensive Cancer Center (CFCCC) or one of the affiliated treatment sites (such as UCI Health Cancer Center – Newport Beach, UCI Health – Yorba Linda Infusion Center, the UCI Health Pacific Breast Center, as well as the Susan Samueli Integrative Health Clinics. Administration of treatment will be conducted at one of the following sites:

- Susan Samueli Integrative Health Clinic – Costa Mesa
- UCI Health – Yorba Linda

- UCI Health – Newport Beach
- UCI Health Pacific Breast Center

B. Study Design

1. Include an explanation of the study design (e.g., randomized placebo-controlled, cross-over, cross-sectional, longitudinal, etc.) and, if appropriate, describe stratification/ randomization/blinding scheme.

This is a randomized sham-controlled, patient and assessor-blinded pilot trial. Participants will be randomized in blocks of 4 to receive either weekly EA (treatment arm) or weekly sham-EA (control arm).

A research assistant who is not involved in the study will perform the allocation to either arm using the computer-generated randomization sequence in a double-blind manner. The participants and outcome assessors are blinded to the treatment allocation, only the acupuncturist will be aware of treatment allocation the randomization codes.

2. Provide precise definitions of the study endpoints and criteria for evaluation; if the primary outcomes are derived from several measurements (i.e., composite variables) or if endpoints are based composite variables, then describe precisely how the composite variables are derived.

Cognitive function – cognitive function will be measured using two types of cognitive assessments.

- Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog v.3.0) – FACT-Cog assesses subjective cognitive impairment. This validated questionnaire contains 33 items in the domains of concentration, functional interference, mental acuity, memory, multitasking and verbal fluency. there are four other scoring subscales: perceived cognitive impairments (PCI; 18 items); perceived cognitive abilities (7 items); impact of perceived cognitive impairment on QOL (4 items); and comments from others on cognitive function (4 items). Both total and PCI scores will be calculated in this study. Total score is calculated by summing scores from all the items and ranges from 0-148, and higher scores represent better subjective cognitive functioning. Similarly, PCI score is calculated by summing responses of all relevant items and ranges from 0 to 72. Overall impairment in self-perceived cognitive function is defined by a reduction of ≥10.6 points in the global score prior to study initiation. In addition, a PCI score of less than 60 will also be used to identify CRCI cases.

- CANTAB® – CANTAB® is a computerised objective assessment containing five tests: reaction time, paired associates learning, spatial working memory, attention switching task, and rapid visual information processing that assesses response speed, learning and memory, working memory, multitasking, and sustained attention. Using International Cognition and Cancer Task Force (ICCTF criteria), overall cognitive impairment is defined as ≥ 2 standard deviations below normative mean on at least 1 cognitive test or ≥ 1.5 standard deviations below normative mean on 2 or more tests. Impairment of each individual CANTAB® domains will be defined as ≥ 1.5 standard deviations below the normative mean. Further, the reliable change index (RCI) score will be calculated using test–retest reliability and the standard error of the difference to control for practice effect in repeated objective cognitive assessments.

Fatigue - Multidimensional Fatigue Syndrome Inventory-Short Form (MFSI-SF) – This validated questionnaire consists of 30 items and has 5 subscales, each with 6 items: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigour. The total score is obtained by subtracting the vigour

subscale from the sum of all the dimensions (total score range from 24 to 96), with a higher score indicating higher fatigue level.

Psychological distress and insomnia - The Rotterdam Symptom Checklist (RSCL) will be used to measure the symptoms that may confound with cognition (such as psychological distress and fatigue). It covers 4 domains: physical symptom distress (23 items), psychological distress (7 items), activity level (8 items) and overall global life quality (single item). Each response is given a 4-point Likert scale. The scores are transformed on a 100-point scale for comparison using the formula: [(raw score-minimum raw score) / (maximum-minimum score) x 100]. Psychological distress is indicated by a score of >16 in the psychological domain. Insomnia is measured by a single item in the checklist.

Quality of Life (QOL) - EORTC QLQ-30 – This validated questionnaire was developed to assess cancer patients' health-related QoL. It incorporates 5 functional scales (cognitive, emotional, physical, role, and social), symptom scales (eg. pain, fatigue, insomnia), and a global health scale. Higher functional, and global health scores, and lower symptom scores represent better quality of life.

Plasma BDNF and cytokine levels - Plasma BDNF and cytokines (IL-1β, IL-4, IL-6, IL_8, IL-10, TNF-alpha) levels will be quantified using commercially available ELISA kits.

Mitochondrial DNA quantification - Mitochondrial DNA, a biomarker for fatigue and oxidative stress will be quantified using the quantitative PCR method.

Recruitment – Recruitment will be evaluated as the number of participants recruited (% of target recruitment) and rate of recruitment per month. Reasons for declining the participation will also be documented.

Compliance – Compliance is measured as the number of acupuncture sessions successfully completed, and proportion (%) of participants completing the acupuncture sessions.

Safety monitoring – Participants will be monitored for adverse events including bruising, pain or discomfort, bleeding and possible infections. Severity of symptoms are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V5.

Blinding and patient acceptance – During the last assessment time point, all study participants will complete a questionnaire evaluating their perceptions towards the EA treatment. Participants will be asked whether they believe that they received EA or sham-EA, if they are satisfied and benefited from the treatment and whether they would consider undergoing treatment again outside of a trial setting.

C. Research Procedures

1. Provide a detailed chronological description of all research procedures.

1. Following completion of informed consent, study participants will be asked to complete a baseline data collection form. Clinical information regarding cancer diagnosis and treatment will be extracted from the patient's medical record by approved study personnel.
2. Following consent into the study, participants will be randomized in blocks of 4 to receive either weekly EA (treatment arm) or weekly sham-EA (control arm). Only the acupuncturist will be aware of the treatment allocation, both participants and assessors will remain blinded.
3. Each participant will attend a total of 10 treatment visits (one visit per week), over the course of 10 weeks. Each EA or sham-EA session will be approximately 1 hour. Participants in the treatment arm will receive EA at 13 standardized acu-points that were chosen for their therapeutic effects.

Participants in the control arm will receive electrical stimulation at non-disease related acu-points. This strategy will overcome the issue that sham-control may elicit placebo therapeutic effects. Table 1 displays more information about the acu-points and procedures of EA and sham-EA. During their visit, patients will be monitored for adverse events such as bruising, pain or discomfort, bleeding, and possible infections. Severity is graded according to the Common Terminology Criteria for Adverse Events V5. Any unanticipated problems will be submitted to the IRB via the unanticipated problems (UP) report as well as to the CFCCC within 5 business days upon the Lead Researcher's knowledge of the event.

Table 1: Treatment procedures and acu-points of EA and sham-EA

Intervention (EA)	**Control (Sham-EA)**
With electrical stimulation	*Non-disease related points with electrical stimulation*
Shenting (GV24), Baihui (DU20), Sinshencong (EX-HN1), Zhongwan (CV12), Guanyuan (CV4), Neiguan (PC6) bilateral, Shenmen (HT7) bilateral, Zusanli (ST36) bilateral, Sanyinjiao (SP6) bilateral, Taixi (KI3) bilateral, Zhaohai (KI6) bilateral, Hegu (LI4) bilateral, Taichong (LIV3) bilateral	Pianli (LI6) bilateral, Wenliu (LI7) bilateral, Fuyang (BL59) bilateral, Kunlun (BL60) bilateral, Sanyangluo (TE8), Sidu (TE9) bilateral, Daheng (SP15) bilateral

The selection of acupoints is based on the experience of experts and previous basic and clinical research. Baihui (DU20), with or without Shenting (GV24), alleviates cognitive impairment by increased antioxidant and anti-inflammatory effects, inhibits NF-κB mediated neuronal cell apoptosis, and enhances expression of BDNF. Baihui (DU20) in combination with Renzhong (GV26), Hegu (LI4), and Zusanli (ST36) can promote the recovery of neurological impairment after traumatic brain injury by activating BDNF/TrkB signaling pathway. Baihui (DU20), Shenting (DU24), Hegu (LI4), Zusanli (ST36) and other acupoints applied in this study including Sishencong (EX-HN1), Taixi (K13), Neiguan (PC6), Taichong (LR3) have shown effectiveness in improving CRCI in several clinical research studies. Zhongwan (CV12) and Guanyuan (CV4) may relieve the degree of fatigue in patients undergo chemotherapy. Zusanli (ST36) in combination with Hegu (LI4), and Sanyingjiao (SP6) or Neiguan (PC6) may effectively improve fatigue. Sanyinjiao (SP6) and Shenmen (HT7) reduce insomnia level through increased GABA and GABA(A)R expression or by reducing the hormones associated with the HPA axis. Zhaohai (KI6) in combination with Sishencong (EX-HN1), Neiguan (PC6), Shenmen (HT7), Zusanli (ST36), Sanyinjiao (SP6), Taichong (LR3) improve depression in cancer patients.

4. Four data collection time points are planned for each participant:(1) baseline, (2) mid-treatment (5 weeks from baseline), (3) end of treatment (10 weeks from baseline), and (4) 4 weeks after end of treatment (14 weeks from baseline). At each time point, 10mL of peripheral blood will be collected for blood biomarkers assessment. Additionally, each participant will complete four questionnaires (FACT-Cog Version 3, MFSI-SF, RSCL, and EORTC QLQ-30) and one computerized cognitive test (CANTAB) to evaluate cognitive function, fatigue level, sleep quality, psychological distress, and quality of life. Figure 1 summarizes the study design and assessment time points for the planned study. Completion of these questionnaires and blood draw will take approximately 45 minutes.
5. At the 14-week visit, participants will also be asked to complete an additional form evaluating their acceptance towards EA and to verify subject blinding maintenance.

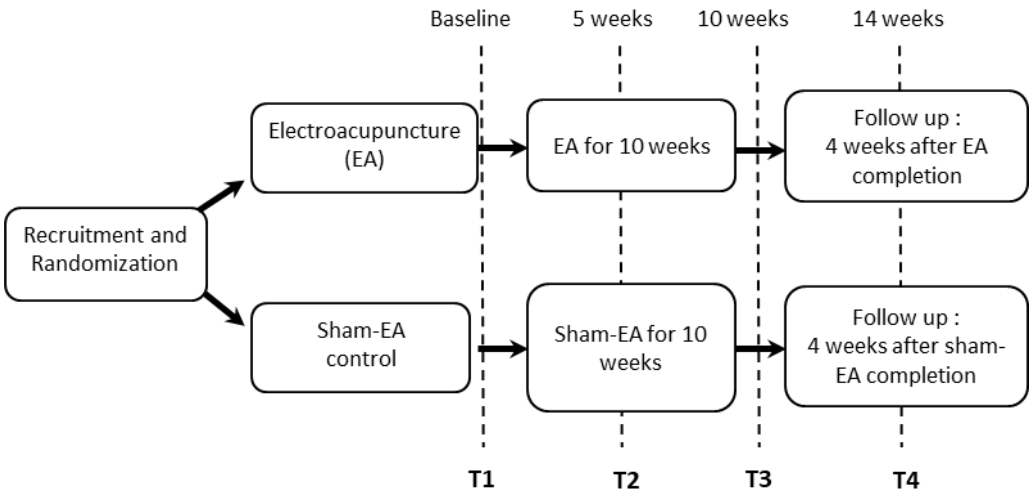

Figure 1: Study assessment time points (T1 denotes time point 1, T2 time point 2 and so on).

2. Describe the duration of a subject's participation in the study. If there are sub-studies, include duration of participation in each sub-study.

The duration of this study is approximately 14 weeks, composed of a 10-week treatment period and a study completion visit at 14 weeks.

3. List data collection instruments (e.g., measures, questionnaires, interview questions, observational tool, etc.).

Investigator-authored, non-standardized, or un-validated measures must be submitted for review.

- Baseline demographics and clinical characteristics data collection form
- Patient acceptance and blinding assessment questionnaire
- Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) Version 3
- Multidimensional Fatigue Syndrome Inventory-Short Form (MFSI-SF)
- Rotterdam Symptom Checklist (RSCL)
- European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
- Cambridge Neuropsychological Test Automated Battery (CANTAB)

D. UCIMC Supplementary Clinical Services

If a UCIMC clinical unit/department (e.g., phlebotomy for blood draws, pharmacy for dispensing study drug(s), radiation services for X-rays, MRIs, CT scans, and Neurology for lumbar punctures) will perform research-related procedures:

1. List the research procedure (e.g. lumbar puncture, MRI, CT Scan), and
2. Identify the unit/department that will perform the procedure.

[ ] Not applicable: This study does not involve the services of a UCIMC clinical unit/department.

Phlebotomy for blood draws.

E. Privacy

Privacy is about the subject's ability to control how much others see, touch, or collect information about the subject. Indicate all of the following methods that will be used to assure subject privacy. *Violations of privacy include accessing a subject's private information without consent, asking personal sensitive information in a public setting, being audio recorded or photographed without consent.*

[X] Research procedures (including recruitment) are conducted in a private room.

[ ] Use of drapes or other barriers for subjects who are required to disrobe.

[X] Only sensitive information directly related to the research is collected about subjects.

[ ] When information is collected from internet sources, the internet site's privacy statement will be reviewed and followed.

Provide a copy of the Data Use Policy to the IRB.

[ ] Other (specify): <Type here>

F. Use of Identifiable Private Information and/or Identifiable Biospecimens as Part of the Main Study

1. For studies that will use **existing identifiable biospecimens** as part of the **main study** (not for determining eligibility):
   a. Indicate the source of the biospecimens and explain how the existing biospecimens will be obtained.
   b. Indicate whether the biospecimens were originally collected for research purposes.

[X] Not applicable: This study does not use existing biological specimens as part of the main study.

How Obtained: Indicate <u>all</u> that apply:
[ ] UCI Health Pathology Biorepository

[ ] Other UCI-Health Entity; specify: <Type here>

[ ] Non-UCI Entity; specify: <Type here>

[ ] Other; explain: <Type here>

Originally collected for research purposes:
[ ] NO – Please explain: <Type here>

[ ] YES – UCI IRB approval granted under IRB protocol number (i.e. HS#): <Type here>

[ ] YES – Non-UCI IRB approval granted. Confirm **<u>one</u>** of the following:

[ ] A copy of the IRB Approval Notice and Consent Form for the original research collection will be submitted with the IRB application (APP). The IRB Approved Consent Form does not preclude the proposed activity.

[ ] A copy of the commercial Vendor Policy or a Letter from the Vendor attesting that the information was collected and will be shared in an appropriate and ethical manner will be submitted with the APP. The vendor's policy does not preclude the proposed activity.

2. For studies that will **use identifiable clinical data** as part of the **main study** (not for determining eligibility), indicate the source and how the study team will access the medical records. *Access to UCI Medical Center medical records for research purposes outside the capacity of the Honest Broker Services, such as access to physician notes, must be obtained from the Health Information Management Services*.

For investigator initiated/authored studies <u>only</u>, submit a data abstraction sheet that includes a complete list of data elements/information that will be collected from (existing) records or submit the case report form (CRF; eCRF).

[ ] Not applicable: This study does not involve the use of identifiable clinical data as part of the main study. *Skip to Section 6.G.*

How Obtained: Indicate <u>all</u> that apply:

[X] The study team will request specific patient information/data from UCIMC Health Information Management Services.

[X] The study team will access their UCI patients' records and abstract data directly from those records.

[ ] The study team will request specific patient information/data from UCI Health Honest Broker Services. Describe the following:

Cohort selection criteria (e.g., use the available Clinical Terms from the Cohort Discovery Tool such as Demographics: Gender, Diagnoses: Asthma, Procedures: Operations on digestive system): <Type here>

Expected cohort size/patient count: <Type here>

Cohort attributes or data elements (e.g., lab test values, medication, etc.): <Type here>

[ ] The study team will request non-UCI Health records and abstract data directly from those records. Describe the following:

Specify the non-UCI Health records that will be screened: <Type here>

Explain how the study team has access to this clinical data: <Type here>

[ ] Other; explain: <Type here>

3. For studies that involve use of existing (i.e. on the shelf; currently available) clinical data, specify the time frame of the clinical data to be accessed (e.g. records from January 2002 to initial IRB approval).

Not applicable.

G. Collection of Photographs, or Audio/Video Recording

1. Describe all procedures involving the use and/or collection of photographs, or audio/video recording.

[X] Not applicable: This study does not involve photographs or audio/video recording. *Skip to Section 6.H.*

2. Specify if photographs or audio/video recording will include subject identifiable information (e.g., name, facial image). If so, indicate which identifiers will be collected.

Not applicable

3. Explain whether the photographs or audio/video recording will be included in subsequent presentations and/or publications and, if so, whether subject identifiers will be included.

Not applicable

H. Sharing Results with Subjects

1. Describe whether individual results (results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subject or others (e.g., the subject's primary care physician). *Only tests ordered by a physician and conducted in a CLIA certified lab may be shared.*
2. Explain what information will be shared and how the results will be shared.

[X] Not applicable: Individual results will not be shared with subjects.

3. Describe whether overall study results will be shared with subjects.
4. Explain how results will be shared.

[ ] Not applicable: Final study results will not be shared with subjects.

[X] The overall study results will be listed on Clinicaltrials.gov. *All Applicable Clinical Trials must be registered.*

[ ] Other: <Type here>

I. Statistical Considerations *(This section is required for Investigator-Authored Research)*

1. Statistical Analysis Plan: Describe the statistical method(s) for the stated specific aims and hypotheses.

The Biostatistics, Epidemiology and Research Design (BERD) Unit under the Institute for Clinical and Translational Science (ICTS) can assist in developing power and sample size calculation. Visit: http://www.icts.uci.edu/services/berd%20request.php for a consultation.

Your analysis plans should match the stated study specific aims and hypotheses in Section 1.

For cancer related research: The Chao Family Comprehensive Cancer Center's Biostatistics Shared Resource (BSR) assists investigators with the design of new studies, power and sample size calculations, and data analyses. To request BSR support, visit: http://www.cancer.uci.edu/bsr

[ ] Not applicable: A statistical analysis plan is not appropriate for this qualitative study design. Plan for assessing study results: <Type here>
Skip to Section 7.

Aim 1: To compare the efficacy of EA versus sham-EA control in reducing cognitive toxicity, fatigue, psychological distress, insomnia, and quality of life.

FACT-Cog, CANTAB, MFSI-SF, RSCL and EORTC QLQ-30 scores will be presented as median, mean, standard deviation, minimum and maximum at each assessment time point. Box plots and histograms will be generated for each score. The number of people with overall cognitive impairment

based on FACT-Cog and CANTAB scores will be presented in counts, percentages, and confidence intervals. All the descriptive statistics and the graphical displays will be constructed for the entire cohort and stratified by treatment allocation.

All the mean scores will be compared before and 5, 10 and 14 weeks after acupuncture therapy for EA and sham-EA control groups. The mean score changes will also be compared between the EA and sham-EA control groups at 5, 10 and 14 weeks after baseline. Biomarkers (BDNF, cytokines and mitochondrial DNA level) changes will be compared between treatment groups.

Mixed effects model, with random intercepts for individual patient, will be generated to evaluate the changes in of symptoms and biomarkers overtime, and its association with the treatment allocation (EA or sham-EA). The covariates of interest will include a treatment indicator (EA vs sham-EA), the duration between the beginning of the latest chemotherapy cycle and the start of EA/sham-EA treatment, the indicator of the EA intervention time point (timept) and the interaction terms which include treatment X duration, treatment X timept, and duration X timept. Patients who have yet to complete their chemotherapy treatment will be imputed with zero for the variable time from end of chemotherapy. Both intention-to-treat and per-protocol analyses will be conducted.

Aim 2: To evaluate the impact of EA versus sham-EA control on biomarkers, including circulating BDNF, pro-inflammatory cytokines (IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-alpha), mitochondrial DNA (oxidative stress indicator), and safety.

Scatter plots of BDNF, cytokines and mitochondrial DNA levels will be plotted against FACT-Cog, CANTAB, MFSI-SF, RSCL, and EORTC QLQ-30 scores. All the descriptive statistics and the graphical displays will be constructed for the entire cohort and stratified by treatment allocation. Mixed effects model, with random intercepts for individual patient, will be generated to evaluate the changes in of symptoms and biomarkers overtime, and its association with the treatment allocation (EA or sham-EA). The covariates of interest will include a treatment indicator (EA vs sham-EA), the duration between the beginning of the latest chemotherapy cycle and the start of EA/sham-EA treatment, the indicator of the EA intervention time point (timept) and the interaction terms which include treatment X duration, treatment X timept, and duration X timept. Patients who have yet to complete their chemotherapy treatment will be imputed with zero for the variable time from end of chemotherapy. Both intention-to-treat and per-protocol analyses will be conducted. Descriptive statistics, presented as counts, percentages, and confidence intervals will be used to analyze the safety outcomes. All the descriptive statistics will be constructed for the entire cohort and stratified by the treatment allocation.

Aim 3: To assess the feasibility of administering EA to manage symptom clusters in cancer patients.

Descriptive statistics will be used to analyze the feasibility outcomes. Categorical variables (participants recruited, acupuncture sessions completed, participants completing all sessions, adverse events, patient responses to acceptability questionnaire) will be analyzed using descriptive statistics and will be presented as counts, percentages, and confidence intervals. All the descriptive statistics will be constructed for the entire cohort and stratified by the treatment allocation.

2. Describe the primary statistical method(s) that will be used to analyze the primary outcome(s) or endpoints.

FACT-Cog scores will be presented as median, mean, standard deviation, minimum and maximum at each assessment time point. Box plots and histograms will be generated. The number of people with overall cognitive impairment based on FACT-Cog will be presented in counts, percentages, and confidence intervals. All the descriptive statistics will be constructed for the entire cohort and stratified by treatment allocation.

FACT-Cog mean scores will be compared before and 5, 10 and 14 weeks after acupuncture therapy for EA and sham-EA control groups. The mean score changes will also be compared between the EA and sham-EA control groups at 5, 10 and 14 weeks after baseline. Mixed effects model, with random intercepts for individual patient, will be generated to evaluate the changes FACT-Cog scores overtime, and its association with the treatment allocation (EA or sham-EA). The covariates of interest will include a treatment indicator (EA vs sham-EA), the duration between the beginning of the latest chemotherapy cycle and the start of EA/sham-EA treatment, the indicator of the EA intervention time point (timept) and the interaction terms which include treatment X duration, treatment X timept, and duration X timept. Patients who have yet to complete their chemotherapy treatment will be imputed with zero for the variable time from end of chemotherapy. Both intention-to-treat and per-protocol analyses will be conducted.

3. Describe the secondary statistical method(s) that will be used to analyze the secondary outcome(s) or endpoints.

CANTAB, MFSI-SF, RSCL and EORTC QLQ-30 scores will be presented as median, mean, standard deviation, minimum and maximum at each assessment time point. Box plots and histograms will be generated for each score. The number of people with overall cognitive impairment based on CANTAB scores will be presented in counts and percentages. Scatter plots of BDNF, cytokines and mitochondrial DNA levels will be plotted against FACT-Cog, CANTAB, MFSI-SF, RSCL, and EORTC QLQ-30 scores. All the descriptive statistics and the graphical displays will be constructed for the entire cohort and stratified by treatment allocation.

All the mean scores will be compared before and 5, 10 and 14 weeks after acupuncture therapy for EA and sham-EA control groups. The mean score changes will also be compared between the EA and sham-EA control groups at 5, 10 and 14 weeks after baseline. Biomarkers (BDNF, cytokines and mitochondrial DNA level) changes will be compared between treatment groups. Mixed effects model, with random intercepts for individual patient, will be generated to evaluate the changes in of symptoms and biomarkers overtime, and its association with the treatment allocation (EA or sham-EA). The covariates of interest will include a treatment indicator (EA vs sham-EA), the duration between the beginning of the latest chemotherapy cycle and the start of EA/sham-EA treatment, the indicator of the EA intervention time point (timept) and the interaction terms which include treatment X duration, treatment X timept, and duration X timept. Patients who have yet to complete their chemotherapy treatment will be imputed with zero for the variable time from end of chemotherapy. Both intention-to-treat and per-protocol analyses will be conducted.

Descriptive statistics will be used to analyze the feasibility and safety outcomes. Categorical variables (participants recruited, acupuncture sessions completed, participants completing all sessions, adverse events, patient responses to acceptability questionnaire) will be analyzed using descriptive statistics and will be presented as counts, percentages, and confidence intervals. All the descriptive statistics will be constructed for the entire cohort and stratified by the treatment allocation. The significance level of 0.05 will be used, and all statistical analyses will be performed using Stata v. 16.

4. If appropriate describe secondary or post hoc analyses of primary outcome(s) or other exploratory analysis.

Not applicable.

5. Sample Size Determination**:** Explain how the overall target sample size was determined (e.g., power analysis; precision estimation), providing justification of the effect size for the primary outcome based on preliminary data, current knowledge/literature and/or cost consideration; if appropriate, provide sample size justification for secondary outcomes. Power analysis should (at least) match the primary outcome/endpoint.
Based on our previous psychometric study of the FACT-Cog questionnaire, a decrease of 6.9-10.6 points (4.7-7.2% of the total score) in the FACT-Cog corresponds to the threshold for clinically significant cognitive deterioration in breast cancer patients. In our previous prospective cohort study, among 131 participants who completed the study, their mean and standard deviation (SD) of FACT-Cog total score at the prior to chemotherapy initiation (T1), 6 weeks following chemotherapy initiation (end of cycle 2; T2), 12 weeks following chemotherapy initiation (end of cycle 4; T3), and approximately 15-months post-chemotherapy initiation (post-chemotherapy evaluation; T4) were estimated to be 132.00 (SD 15.65), 130.23 (19.44), 128.51 (19.93) and 127.53 (21.89), respectively. Assuming the correlation between observations on the same participant across time is 0.2 and a common standard deviation of two groups is 20.5, with 29 evaluable participants per group, a total of 58 evaluable participants, a power of 80% will be achieved to detect the difference of 9.6 in means of FACT-Cog total score between two groups across 4 time points with a significant level of 0.05. After accounting a potential 10% attrition, sixty-four eligible patients will be enrolled into the study.

SECTION 7: RISK ASSESSMENT AND POSSIBLE BENEFITS

A. Risk Assessment

1. Indicate the appropriate level of review of this study, based upon your risk assessment.
[X] This study involves greater than minimal risk to subjects and requires Full Committee review. *Skip to Section 7.B.* **[ ]** This study involves no more than minimal risk and qualifies as **Expedited research**.
2. If this study involves no more than minimal risk, provide justification for the level of review and for all applicable Expedited Categories you have chosen.
Not applicable.

B. Risks and Discomforts

1. Describe and assess any reasonably foreseeable risks and discomforts — physical, psychological, social, legal or other. Include an assessment of their expected frequency (e.g., common – 65%, less common – 40%, unlikely – 5%, rare - <1%) and the seriousness (mild, moderate, severe). *A bullet point list is recommended. If this study will involve the collection of identifiable private information, even temporarily, for which the disclosure of the data outside of the research could reasonably place the subjects at risk, include the risk of a potential breach of confidentiality.*
The patients are not restricted from receiving any standard therapies they may be on for the duration of the study.

EA and Sham-EA Treatment Risks:
The current and frequency used are very low and participants will likely only experience a slight tingling feeling. Electroacupuncture has a very low incidence of side effects. This is, in part, because the diameter of acupuncture needles is very small (0.20-0.25 mm, which is equivalent to 32 gauge). The needles used in the acupuncture are new, sterile needles so there is no chance of contracting a disease, such as AIDS or hepatitis as a result of this study.

Foreseeable risks and discomforts include:

Likely
- Very mild discomfort might occur during removal of the electrodes stuck to the skin.
- Mild discomfort including a feeling of heaviness, swelling, soreness, or numbness
- The presence of <1-2 drops of blood following needle removal

Less Likely
- Slight pain, bruising, bleeding or discomfort may occur from needle insertion and removal.

Rare
- Infection at needle insertion site

Severity of adverse events will be graded according to the Common Terminology Criteria for Adverse Events V5, as follows:

Bruising – A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.
- Grade 1: Localized or in a dependent area
- Grade 2: Generalized

Pain - A disorder characterized by the sensation of marked discomfort, distress or agony.
- Grade 1: Mild pain
- Grade 2: Moderate pain; limiting instrumental activities of daily living
- Grade 3: Severe pain; limiting self care activities of daily living

Skin Infection - A disorder characterized by an infectious process involving the skin such as cellulitis.
- Grade 1: Localized, local intervention indicated
- Grade 2: Oral intervention indicated (e.g. antibiotic, antifungal, or antiviral)
- Grade 3: IV antibiotic, antifungal, or antiviral intervention indicated
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death

Randomization: Study participants will be allocated randomly to either the EA or sham-EA arm. The sham-EA is chosen as control to account for potential biases and placebo effects. A research assistant who is not involved in the study will perform the allocation to either arm using the computer-generated randomization sequence in a double-blind manner. The participants and outcome assessors are blinded to the treatment allocation, only the acupuncturist will be aware of treatment allocation the randomization codes.

Control: During this study there is a 50% chance that participants will receive sham-EA treatments. This could lengthen the amount of time before they receive a treatment that may be effective. During this time participants may experience worsening of their condition, including increased symptoms such as cognitive

issues. The researchers will carefully monitor participants' condition. If participants' symptoms worsen and make them uncomfortable, they can withdraw from the study.

Blood draw: Removing blood by a needle may cause temporary pain, bruising, bleeding, swelling, dizziness, and on rare instances fainting or infection.

Psychological discomforts: Some of the procedures may cause embarrassment or anxiety, or the questions the researchers ask participants may be upsetting or make them uncomfortable. If participants do not wish to answer a question, they can skip it and go to the next question. If participants do not wish to participate you can stop.

Reproductive Risks: Participants should not get pregnant while in this study. The EA/sham-EA used in this study could harm an unborn baby. Participants should also not breastfeed a baby while in this study.

2. Discuss what steps have been taken and/or will be taken to prevent and minimize any risks/ potential discomforts to subjects. *Examples include: designing the study to make use of procedures involving less risk when appropriate; minimizing study procedures by taking advantage of clinical procedures conducted on the subjects; mitigating risks by planning special monitoring or conducting supportive inventions for the study; implement security provisions to protect confidential information.*

If a patient becomes pregnant during the study, there may be unknown risks to the unborn child. By signing the consent form, the patient confirms to the best of her knowledge that she is not pregnant now, nor does she intend to become pregnant (or nurse an infant) during involvement in the study. Women of childbearing potential should use a medically acceptable form of birth control during her participation in the study. The acting physician and the patient will discuss available methods.

During explanation of the study procedures to study participants, clear instructions will be provided regarding all aspects of the study, including the randomization procedure, the EA and sham-EA treatment, blood drawing and questionnaires. The acupuncturist will show the participant the small acupuncture needles and will explain the procedures of the study, including the low current stimulation, and the feelings that they may encounter when needles are inserted into the acupoints, etc. This type of explanation helps to mitigate the psychological stress experienced by some patients.
All questions and concerns raised by participants will also be addressed by the study team member prior to initiation of any study procedures. Furthermore, all study personnel will complete the UCI Human Subjects and HIPAA training required by the IRB of all individuals working on studies that require contact with human subjects. All study personnel will be trained in confidentiality protocol procedures.

To ensure data confidentiality, the CANTAB data set will be coded without subject identifiers and will be stored in secured servers hosted by CANTAB with 2 levels of password protection for access to the iPad itself and the CANTAB application. Only key study personnel will have access to the device that is secured in a locked file cabinet in locked office at the Pharmacy Department. All hardcopy questionnaires will be coded without subject identifiers and stored in the locked office at the Pharmacy Department. Only investigators based in the study sites will have access to the iPad or the questionnaires. The code key will be kept separately and encrypted with password protection and stored electronically in highly secure and HIPAA-compliant servers hosted by UC Irvine with access limited to key study personnel.

Data and Safety Monitoring Plan

This is a **risk level 3 study**, as defined in the Chao Family Comprehensive Cancer Center (CFCCC) Data and Safety Monitoring Plan (DSMP) because it is an investigator-initiated interventional trial with minimal risk.

The Principal Investigator (PI), co-investigator, clinical research coordinator, and statistician are responsible for monitoring of data and safety for this study. For studies that have stopping rules for safety and efficacy, the PI will be responsible for the implementation and make changes as applicable. The CFCCC Data and Safety Monitoring Board (DSMB) is an independent body responsible for the safety of study subjects as well as the data integrity of the protocol. Data and safety will be reported to the DSMB with submission of progress reports that include aggregated reports of adverse events, serious adverse events, deviations, and violations. In addition, certain adverse events, serious adverse events, deviations, violations, and unanticipated problems will be reported promptly to the DSMB for review according to the tables below.

The CFCCC Stern Center for Cancer Clinical Trials and Research Quality Assurance Unit will conduct monitoring and auditing activities as per the UC Irvine CFCCC Quality Assurance Monitoring and Auditing Plan and at the discretion of the CFCCC DSMB in order to ensure patient safety and data integrity oversight. By conducting internal monitoring and auditing, the CFCCC will ensure compliance with high quality standards and all applicable regulations, guidelines, and institutional policies. Trial monitoring and auditing may be completed remotely or on-site.

Risk Levels

Risk Level	Definition	Monitoring
Level 1	**High Risk** - UCI investigator-initiated interventional trials for which the PI holds Investigational New Drug (IND) or Investigation Device Exemption (IDE). Example: Gene therapy, dendritic cell products from GMP suite, phase I/II development and phase I studies, first in human, etc.	Two months after subject enrollment
Level 2	**Medium Risk** - UCI investigator-initiated interventional trials for which IND/IDE is exempt by FDA. Example: Use of commercially available agents for an unapproved indication.	Six months after subject enrollment
Level 3	**Low Risk –** UCI investigator-initiated interventional trials that are minimal risk. Example: Phase III clinical studies, dietary intervention trials, and after-market studies.	Twelve months after subject enrollment
Exempt	Studies that are industry-sponsored, NCTN-sponsored, and/or trials that are monitored by an external DSMB.	

Recording of Events

Adverse events, serious adverse events, deviations, violations, and unanticipated problems must be entered into the clinical trial management system (CTMS), OnCore. Adverse events and serious adverse events will be collected from the time the research patient begins treatment until 4 weeks after

the end of treatment. All adverse events/serious adverse events should be followed until resolution or stabilization.

Event Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [Modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) [21 CFR 312.32] - defined as any expected or unexpected adverse event that result in any of the following outcomes:

- Death
- Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) - Any incident, experience or outcome that meets all three of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; AND
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Protocol Violation - A protocol violation is an accidental or unintentional change to or noncompliance with the IRB-approved protocol that increases risk or decreases benefit and/or affects the subject's rights, safety, welfare, and/or the integrity of the data. Examples of incidents that may be considered violations include: enrolling a participant who does not meet the inclusion criteria; obtaining verbal consent before the initiation of study procedures when the IRB requires signed, written informed consent; and failure to collect screening labs before initiation of study procedures [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Protocol Deviation - a protocol deviation is an accidental or unintentional change to the research protocol that does not increase risk or decrease benefit or have a significant effect on the participant's rights, safety or welfare, or on the integrity of the data. Deviations may result from the action of the participant, researcher, or staff. Examples: a rescheduled study visit, an omitted routine safety lab for a participant with previously normal values; or failure to collect an ancillary self-report questionnaire data (e.g., quality of life) [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Reporting Requirements to the CFCCC DSMB

Unanticipated Problems

Event Type	Reporting Timeframe
Unanticipated Problems	5 business days from the date the PI is aware of the event

Adverse Event/Serious Adverse Events

Event Type	Reporting Timeframe
Serious Adverse Events (all attributions) that meet all of the following criteria: ▪ Unexpected ▪ Grades 3-5 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event
Adverse Events that meet all of the following criteria: ▪ Unexpected ▪ Study related (possibly, probably, or definitely) ▪ Grades 3-4 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event
All other Adverse Events and Serious Adverse Events should be reported as noted in the 'Recording of Events' section	Prior to each scheduled progress review
** Investigators are not obligated to actively seek information regarding the occurrence of new AEs or SAEs beginning after the 30-day post-treatment period. However, if the investigator learns of such an event and that event is deemed relevant to the study, he/she should promptly document and report the event.*	

Deviations/Violations

Event Type	Reporting Timeframe
Violations as defined above (e.g. wrong dosage of drug administered, safety procedures not being conducted at specific time points)	5 business days from the date the PI is aware of the event

Deviations as defined above, including: ▪ Planned deviations (e.g. rescheduling a visit that will be out of window due to a holiday) ▪ Unplanned deviations (e.g. rescheduled visit, a missed routine safety laboratory test for a participant with previously normal values)	Prior to each scheduled progress review

Reporting Requirements to UCI IRB
Report adverse events, serious adverse events, violations, and deviations within 5 business days if the event/incident met the criteria for an unanticipated problem (UP). The current policy can found at the following link: UCI Office of Research

Recording of Events

- The participating institution must enter the above events into OnCore, according to the reporting requirements of the CFCCC DSMB noted above.

Quality Assurance

- The coordinating center PI (sponsor) is primarily responsible for ensuring the study is conducted according to the investigational plan and protocol.
- Quality Assurance activities (QA monitoring and auditing) will be conducted as per UC Irvine Chao Family Comprehensive Cancer Center Quality Assurance Monitoring and Auditing Plan in order to ensure patient safety and data integrity oversight.
- The participating institution should follow their own internal quality assurance policies in order to monitor patient safety and data integrity oversight.
- The participating institution must permit study-related monitoring and auditing and provide access to study-related materials. Trial monitoring and auditing will be performed by the UC Irvine CFCCC Stern Center for Cancer Clinical Trials and Research Quality Assurance Unit.
- Trial monitoring and auditing may be completed remotely or on-site.

C. Potential Benefits

1. Describe the potential benefits subjects may expect to receive from participation in this study. *Compensation is not a benefit; do not include it in this section.*

[ ] There is no direct benefit anticipated for the subjects.

If participants are randomized to the group that receives EA and it proves to treat their condition more effectively than the sham-EA, they may benefit from participating in the study, but this cannot be guaranteed.

2. Specify the expected potential societal/scientific benefit(s) of this study.

This study will help researchers learn more about EA, and it is hoped that this information will help in the treatment of future cancer patients with complex cancer symptoms.

SECTION 8: ALTERNATIVES TO PARTICIPATION

Describe the alternatives to participation in the study available to prospective subjects. Include routine (standard of care) options as well as other experimental options, as applicable.

[ ] No alternatives exist. The only alternative to study participation is not to participate in the study.

[ ] There are routine standard of care alternatives available; specify: <Type here>

[X] There are other alternatives to study participation; specify:

There are no standard of care alternatives available that study participation would preclude participants from utilizing, however, individuals may have the option to participate in another experimental clinical study if one is available.

SECTION 9: SUBJECT COSTS

1. Indicate below if subjects or their insurers will be charged for study procedures. Identify and describe those costs.

[ ] Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 10.*

[X] This study involves interaction/intervention with research subjects; however there are no costs to subjects/insurers.

[ ] This study involves interaction/intervention with research subjects, and there are costs to subjects/insurers: <Type here>

2. If subjects or their insurers will be responsible for study-related costs, explain why it is appropriate to charge those costs to the subjects or their insurers. Provide supporting documentation as applicable (e.g., study procedures include routine (standard of care) procedures; FDA IDE/HDE/IND letter that supports billing to subjects).

[X] Not applicable: The study involves no costs to subjects for study participation.

[ ] Study related costs will be billed to subjects or their insurers for the following reasons: <Type here>

SECTION 10: SUBJECT COMPENSATION AND REIMBURSEMENT

1. If subjects will be compensated for their participation, explain the method/terms of payment (e.g., money; check; extra credit; gift certificate).

[ ] Not applicable: This study involves no interaction/intervention with research subjects. *Skip to Section 11.*

[ ] No compensation will be provided to subjects.

[X] Compensation will be provided to subjects in the form of cash/gift certificate.

[ ] Compensation will be provided to subjects in the form of a check issued to the subjects through the UCI Accounting Office. The subject's name, address, and social security number, will be released to the UCI Accounting Office for the purpose of payment and for tax reporting to the Internal Revenue Service (IRS).

[ ] Other: <Type here>

2. Specify the schedule and amounts of compensation (e.g., at end of study; after each session/visit) including the total amount subjects can receive for completing the study. *Compensation should be offered on a prorated basis when the research involves multiple visits.*

   For compensation ≥ $600, subject names and social security numbers must be collected. This information must be reported to UCI Accounting for tax-reporting purposes.

[ ] Not applicable: This study involves no compensation to subjects.

Subjects will be compensated with the following schedule and amounts:

Participants will be paid $20 at 5 weeks into the treatment, $10 for completion of the treatment and $10 after the final study visit at 4 weeks after the end of the treatment. Total compensation for participation in the entire study is $40. If the subject decide to withdraw from the study or are withdrawn by the research team, they will receive compensation for the visits and/or procedures that they have completed.

3. Specify whether subjects will be reimbursed for out-of pocket expenses. If so, describe any requirements for reimbursement (e.g., receipt).

[X] Not applicable: This study involves no reimbursement to subjects.

Subjects will be reimbursed; specify: N/A

SECTION 11: CONFIDENTIALITY OF RESEARCH BIOSPECIMENS/DATA

A. Information and/or Biospecimens Storage

1. Indicate how information and/or biospecimens will be stored and secured. Check all that apply:

[X] Information will be maintained electronically. Information will be password protected and maintained in an encrypted format. *Researchers may access UCI-contracted data sharing and storage tools through UCI OIT.*

[X] Information will be maintained in hard copy. Information will be stored in a locked area that is not accessible to non-study team members.

[X] Biospecimens will be stored in a locked lab/refrigerator/freezer that is not accessible to non-study team members.

2. List the location(s) where the data and/or biospecimens will be stored**.**

Biospecimens will be stored at The Chao Family Comprehensive Cancer Center.

3. Indicate all subject identifiers that may be retained with the information and/or biospecimens collected for the research study. *If any study-related data will be derived from a medical record, added to a medical record, created or collected as part of health care, or used to make health care decisions the HIPAA policy applies. The subject's HIPAA Research Authorization is required or a waiver of HIPAA Research Authorization must be requested by completing Appendix T.*

[ ] This study does not involve the collection of subject identifiers.

Check all the following identifiers will be used, created, collected, disclosed as part of the research:

[ ] Names	**[ ]** Social Security Numbers	**[ ]** Device identifiers/Serial numbers
[X] Dates*	**[X]** Medical record numbers	**[ ]** Web URLs
[ ] Postal address	**[ ]** Health plan numbers	**[ ]** IP address numbers
[ ] Phone numbers	**[ ]** Account numbers	**[ ]** Biometric identifiers
[ ] Fax numbers	**[ ]** License/Certificate numbers	**[ ]** Facial Photos/Images
[ ] Email address	**[ ]** Vehicle id numbers	**[ ]** Any other unique identifier

[ ] Other (Specify all): <Type here>

* *birth date, treatment/hospitalization dates*

4. Indicate if a code will be used to link subject identifiers with the information and/or biospecimens.

[ ] Not applicable: No subject identifiers will be collected.

[X] A code will be used (i.e. information and/or biospecimens will be coded). Subject **identifiers** will be **kept separately** from the information and/or biospecimens. The code key will be destroyed at the earliest opportunity, consistent with the conduct of this research.

[ ] A code will not be used. Subject **identifiers** will be **kept directly** with the information/biospecimens.

5. If **subject identifiable data** will be transported or maintained on **portable devices**, explain why it is necessary use these devices. *Only the "minimum data necessary" should be stored on portable devices as these devices are particularly susceptible to loss or theft. If there is a necessity to use a portable device for the initial collection of identifiable private information, the research files must be encrypted, and subject identifiers transferred to a secure system as soon as possible.*

[X] Not applicable: Research data will not be transported or maintained on portable devices.

[ ] Research data will need to be maintained on the following portable device(s) for the following reason(s): <Type here>

B. Information and/or Biospecimens Access

1. Specify who will have **access to subject identifiable information and/or identifiable biospecimens** as part of this study. Check all that apply.

[ ] Not applicable: No subject identifiers will be collected.

[X] Authorized UCI personnel such as the research team and appropriate institutional officials, the study sponsor or the sponsor's agents (if applicable), and regulatory entities such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), and the National Institutes of Health (NIH).

[ ] Other: <Type here>

2. Specify whether subject identifiers be disclosed in presentations and/or publications.

[ ] Not applicable: No subject identifiers will be collected.

[X] Subject identifiers will **not** be disclosed.

[ ] Subject identifiers will be disclosed. Text regarding the disclosure will be included in the consent document and specific permission to disclose will be discussed with subjects.

3. Specify whether **information and/or biospecimens be shared** with other researchers **outside of the study team** (i.e., UCI / non-UCI researchers) for secondary research purposes. *When accessing/transferring data from/to a non-profit, please contact Grace J. Park at parkgj@uci.edu. When accessing/transferring data from/to a for-profit, please contact the Industry Contract Officer at UCI Beall Applied Innovation assigned to your department.*

[ ] Not applicable: information and/or biospecimens will not be shared.

[ ] Identifiable information and/or identifiable biospecimens may be shared. Text regarding the information/specimens sharing will be included in the consent document and specific permission to share information will be discussed with subjects.

Check one of the following:

[ ] A biorepository will be established and manage by the UCI study team. ***Submit Appendix M.***

[ ] Subject identifiers will be retained in an established non-UCI biorepository (i.e. not managed by the UCI study team). The non-UCI biorepository has a current IRB approval on file. Specify the non-UCI biorepository: <Type here>

[X] De-identified information and/or de-identified biospecimens may be shared (i.e. research participants cannot be identified by other researchers). Text regarding the information/biospecimens sharing will be included in the consent document, as applicable.

Check one of the following:

[X] No subject identifiers will be retained by the study team beyond initial collection (i.e. information/biospecimens cannot be linked to an individual and a key code does not exist). Requests for de-identified information and/or de-identified biospecimens will be managed by the UCI study team.

[ ] Subject identifiers will be retained by the study team beyond initial collection (i.e. information/biospecimens can be linked to an individual and/or a key code exists). A biorepository will be established and managed by the UCI study team. ***Submit Appendix M.***

[ ] Subject identifiers will be retained by the study team beyond initial collection (i.e. information/biospecimens can be linked to an individual and/or a key code exists). De-identified information/biospecimens will be retained and managed in an established non-UCI biorepository (i.e. not managed by the UCI study team). The study team will remove any information that could potentially allow for the re-identification of participants prior to sending the information/biospecimens to the non-UCI biorepository. Specify the non-UCI biorepository: <Type here>

[ ] Other: <Type here>

C. Research Information and/or Biospecimens Retention

1. Indicate how long research information and/or biospecimens will be retained.
2. If more than one option applies, indicate accordingly.
3. If research involves Protected Health Information (PHI): Investigators must destroy PHI at the earliest opportunity, consistent with the conduct of this study, unless there is an appropriate justification for retaining the identifiers or as required by law. Otherwise, identifiable data is to be retained as noted below.

UPDATED! In accordance with UCOP policy, information/biospecimens will be retained for 10 years after the end of the calendar year in which the research is completed, unless otherwise specified in the award agreement. Choose the longest retention period applicable to the study:

[X] There is no contract or award associated with this research. Information/biospecimens will be retained for 10 years after the end of the calendar year in which the research is completed.

[ ] The contract or award associated with this research requires that information/biospecimens be retained for the following period; specify time frame: <Type here>.

[ ] The study is conducted under an IND or an IDE investigation, information/biospecimens will be retained for two years after an approved marketing application. If approval is not received, the information/biospecimens will be kept for 2 years after the investigation is discontinued and the FDA is notified per FDA sponsor requirements.

[ ] This research includes the potential for future **secondary research using information/biospecimens** which will be stored and maintained indefinitely.

D. Audio/Video Recordings & Photographs

1. If subject identifiable audio/video recordings will be collected, specify the timeframe for the transcription and/or de-identification. 2. If subject identifiable photographs will be collected, specify the timeframe for de-identification.
UPDATED! **[X] Not applicable**: Identifiable audio/video recordings and/or photographs will not be collected. **Transcription:** **[ ]** Audio/video recordings transcribed; specify time frame: <Type here> **[ ]** Audio/video recordings will NOT be transcribed; specify why: <Type here> **De-Identification:** **[ ]** Subject identifiable audio/video recordings & photographs will be de-identified; • specify time frame: <Type here> • specify how (ex. real name replace with pseudonym during transcription; blurred facial features): <Type here> **[ ]** Subject identifiable audio/video recordings & photographs will NOT be de-identified; specify why: <Type here>

E. Certificate of Confidentiality

1. Indicate whether a Certificate of Confidentiality (CoC) has been or will be requested.
[X] Not applicable: No CoC has been requested for this study. **[ ] This is a non-NIH funded/supported study. Choose one of the following:** **[ ]** A CoC will be requested for this study. *The CoC application must be submitted to the IRB staff for review after IRB approval.* **[ ]** A CoC has been obtained for this study. *Provide a copy of the CoC Approval Letter.* The expiration date of this CoC is: <Type here> **[ ] This is an NIH funded/supported study** and a CoC will be automatically issued for studies that involve identifiable, private, and sensitive information.
2. Explain in what situations the UCI study team will disclose identifiable private information protected by a CoC.
Not applicable.